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MYERS, CARLA J	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	09/424,629	FOOTE ET AL.
	Examiner	Art Unit
	Carla Myers	1634

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18 and 24-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-18, 24-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to the amendment filed November 3, 2004 . Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claim Rejections - 35 USC § 103

2 . Claims 1-7, 10, 17, 18, 24-30, 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb (U.S. Patent No. 5,869,242) in view of Koster (U.S. Patent 6,500,621). In view of the amendments to change the dependency of the claims, this rejection now also applies to claims 11-16.

Kamb teaches methods for detecting a mutation, polymorphism or other type of nucleotide variation in a nucleic acid molecule. In the method of Kamb, differences in the nucleotide composition and / or length of a nucleic acid molecule are identified using MALDI MS to compare the mass spectra of the nucleic acid to a reference nucleic acid (see column 2). In particular, Kamb (column 2, lines 48-59) teaches that variations in a nucleic acid sequence can be detected by a method comprising preparing "amplified DNA from a patient's sample in the region of a known mutation. The amplified DNA is then analyzed in a mass spectrometer to determine the mass of the amplified fragment. The mass spectrum obtained is compared to the mass spectrum of fragments obtained from known samples of either wild-type genes or genes containing the known mutation. These known spectra are referred to as "signature" spectra. A simple comparison of the sample spectrum vs. signature spectra will reveal whether the patient's DNA contains a

mutation." Kamb further teaches that a "variation of the above technique may also be used to analyze for polymorphisms. In this variation the fragments of nucleic acid are digested via any one of several techniques to smaller fragments which may range from one base up to approximately 50 bases. The resulting mix of fragments is then analyzed via mass spectrometry. The resulting spectrum contains several peaks and is compared with signature spectra of samples known to be wild-type or to contain a known polymorphism." (see column2, line 65 to column 3, line 6).

Accordingly, Kamb teaches that any art conventional method of specific digestion can be used to detect the presence of a nucleotide variation. In one embodiment of the method, Kamb teaches that the digestion step may be performed with a restriction endonuclease (see, for example, column 6). In another embodiment, Kamb teaches that a ribonuclease may be used to detect the presence of nucleotide variation in a sample RNA. Specifically, Kamb (column 10) teaches digestion of RNA using ribonuclease T1, which hydrolyzes RNA on the 3' side of G residues. Ribonuclease T1 digestion is considered to be "single-base-specific cleavage" since the enzyme recognizes and cleaves specifically between the guanosine 3'-phosphate residue and the 5'OH residue of adjacent nucleotides. While Kamb teaches that the oligonucleotides and oligonucleotide fragments present following the cleavage reaction are analyzed using MS, and particularly MALDI MS, Kamb does not specifically teach analyzing the oligonucleotides using MALDI-TOF MS.

However, Koster teaches methods for detecting the presence of a mutation or polymorphism wherein the methods comprise cleaving a nucleic acid with one or

specific endonucleases to form a mixture of fragments and comparing the molecular weights of test fragments with the molecular weights of wildtype and mutant fragments using MALDI-TOF MS (see column 18, lines 54-58). Koster (column 3) teaches that "MALDI mass spectrometry, in contrast, can be particularly attractive when a time-of-flight (TOF) configuration is used as a mass analyzer...Since, in most cases, no multiple molecular ion peaks are produced with this technique, the spectra, in principle, look simpler compared to ES mass spectrometry." Koster (column 28) teaches that MALDI TOF MS can distinguish between oligonucleotides that differ in length by one nucleotide and provides a fast and reliable means for analyzing nucleic acids.

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have practice the method of Kamb using the MALDI TOF MS technique to analyze the digested and undigested oligonucleotides because Koster teaches that MALDI TOF MS provides an effective and rapid means for detecting and distinguishing between oligonucleotide fragments based on their size and composition and MALDI TOF MS provides a simpler spectra to interpret as compared to other types of mass spectrometry.

With respect to claim 2, Kamb (column 10) teaches that the sample RNA to be used for analysis is prepared by amplifying fragments of DNA, cloning the fragments into vectors containing RNA polymerase promoters and synthesizing RNA transcripts. At column 4 (lines 2-8), Kamb teaches that DNA amplification is accomplished by PCR.

With particular respect to claims 6, 7, 31 and 33, Kamb (see, for example, column 2, lines 53-64; column 5, lines 5-61) teaches that the presence of a nucleotide

variation can be detected by direct analysis of oligonucleotides or by base-specific digestion of oligonucleotides and Kamb teaches that the method is applicable to simultaneously detecting multiple variations. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have practiced the method of Kamb so as to have detected both variations that result in a change in a cleavage site and variations which do not result in a change in a cleavage site in order to have allowed for the analysis of a wider variety of variations and to have allowed for the detection of multiple variations in the oligonucleotide being analyzed or to have identified variations that do not lead to a change in a cleavage site.

Further, Kamb (column 4, lines 36-41) states that in one embodiment, it is beneficial "to incorporate deoxyuridine into amplified DNA. This is useful for producing small fragments by later digesting the amplified DNA with uracil-N-glycosidase." Kamb discusses the benefit of analyzing smaller fragments of nucleic acids. For instance, at column 3 (lines 49-55), Kamb states that "There is no need to analyze fully the complete gene sequence of a gene associated with a disease...Rather one can use a method which is exquisitely precise in determining the total composition of fragments. Mass spectroscopy is one such method which yields very precise results and is applicable to short nucleotide fragments. " Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have incorporated deoxyuridine into the sample nucleic acid during PCR, and to have cleaved the PCR products using uracil-N-glycosylase prior to performing MALDI TOF MS in order to have achieved the benefits stated by Kamb of generating shorter fragments that could be readily analyzed

by mass spectrometry and which would allow for the detection of the presence of a mutation or polymorphism in the nucleic acid sample.

With respect to claims 10-18 and 34, Kamb does not specifically teach a computer program to control the method of detecting a difference in one or more nucleotides of a sample nucleic acid as compared to a reference nucleic acid. However, Kamb (column 11) does teach that "(m)ass spectrometers are presently available which have target slides with 64 sample spots that can be deposited by a robot" and that use of such an automated system provides for the rapid analysis of nucleic acid samples. Further, Koster (column 2, lines 40-46) states that "Due to the apparent analytical advantages of mass spectrometry in providing high detection sensitivity, accuracy of mass measurements, detailed structural information by CID in conjunction with MS/MS configuration and speed, as well as on-line data transfer to a computer, there has been considerable interest in the use of mass spectrometry for the structural analysis of nucleic acids." Additionally, the use of computer programs to control methods and store data obtained from nucleic acid analysis, particularly MALDI MS analysis, was conventional in the art at the time the invention was made. Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a computer program to control the method of detecting a nucleotide variation in a nucleic acid sample in order to have provided a convenient and rapid means for storing and analyzing the data obtained from the detection method and / or for automating the detection method.

RESPONSE TO ARGUMENTS:

In the response filed November 3, 2004, Applicants traversed the above rejection by arguing that Kamb's method of detecting a mutation is limited to instances in which prior knowledge of the mutation is available. Applicants assert that Kamb does not teach that the digestion fragments should be analyzed by MALDI TOF.

Applicants arguments have been fully considered but are not persuasive to overcome the present grounds of rejection. Applicants response separately addresses each of the cited reference. Such arguments are entitled to little weight, where, as here, the rejection is based upon the combined disclosure of the references. In re Keller, 642 F.2d 413, 208 USPQ 871 (CCPA 1981). The test of obviousness under 35 U.S.C. 103 is not express suggestion of the claimed invention in any or all of the references but what references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them (In re Rosselet, 146 USPQ 183(CCPA 1965).

In the present situation, the teachings of Kamb and Koster when considered as a whole would have suggested the claimed invention to one of ordinary skill in the art. As discussed above, Kamb teaches a method for detecting a difference in one or more nucleotides by digesting a sample nucleic acid using any art conventional technique and analyzing the mixture of digestion fragments by MALDI MS, wherein an altered peak pattern as compared to a reference nucleic acid indicates the presence of a difference in one or more nucleotides. Kamb also teaches that one method for digesting the sample nucleic acid is to employ ribonuclease T_1, which is a single-base specific cleavage enzyme. While Kamb does not teach analyzing the resulting digestion products with MALDI TOF, Koster teaches methods for analyzing nucleic acid digestion

products with MALDI TOF and teaches the benefits of using MALDI TOF over MALDI MS. Accordingly, when taken as a whole, the combined prior art would have suggested the claimed invention of detecting a difference in one or more nucleotides by digesting the nucleic acid with a single-base specific cleavage enzyme (ribonuclease T_1) and analyzing the digestion fragments by MALDI TOF.

Applicant's characterization of Kamb as teaching only methods which detect a known mutation does not take into consideration of the complete teachings of Kamb. Contrary to Applicants arguments, the teachings of Kamb are not limited to methods which require cleavage at the point of a mutation in order to distinguish a mutated fragment from a wildtype fragment. Rather, Kamb teaches that mutations can be detected by digesting RNA with ribonuclease T_1, which cleaves 3' to G. Further, Kamb teaches how to analyze a combination of digestion fragments. At columns 8-9, Kamb teaches methods in which a nucleic acid sample is digested with DNaseI (i.e., an enzyme which is not a restriction enzyme, and which does not cleave exclusively at a point mutation site). Kamb teaches that the digestion fragments are analyzed by comparing the sample peaks with peaks from reference nucleic acids wherein an altered peak relative to the reference nucleic acid is indicative of a difference in one or more nucleotides.

Applicants assert that the method of Kamb requires the use of primers and thereby requires knowledge of the location of the mutation. Such an assertion does not distinguish the claimed invention over that suggested by the combined prior art. The present claims recite the use of the claim language "comprising" and thereby also allow

for the use of primers to generate the nucleic acids to be analyzed. Further, present claims 2 and 25 specifically require that the sample nucleic acid is amplified by PCR prior to analysis. Applicant's response asserts that the claimed invention is distinguishable over that of Kamb and Koster in that the method is applicable to large nucleic acid molecules. However, the majority of claims are not limited to the analysis of nucleic acids of any particular length. Those claims which do recite a size limitation allow for the analysis of nucleic acid fragments of about 4 to 100 bass, 2 to 1000 bases, or 3 to 500 bases. Both Kamb and Koster teach the analysis of nucleic acids within this size range.

Applicants further assert that the claimed invention is distinguishable over the method of Kamb and Koster because the method does not require prior knowledge of the mutation to be detected. However, the present claims do not recite any limitations which require that the mutation to be detected is at an unknown location in the sample nucleic acid. Rather, the claims require only the use of single-base specific cleavage. Kamb teaches this limitation in that Kamb teaches digestion of the nucleic acid with ribonuclease T_1. Further, Koster teaches that nucleic acids to be analyzed MALDI TOF can be digested using any art conventional means. Additionally, the claims require that the peaks obtained for the sample nucleic acid are compared to the peaks obtained from a reference nucleic acid. This is the same methodology employed by Kamb and Koster. Accordingly, the mutations detected by the claimed invention are not distinguishable from the mutations detected by the combined methods of Kamb and Koster.

Applicants state that while Kamb discusses digestion with uracil-N-glycosylase, Kamb does not teach how to use uracil-N-glycosylase to detect a difference in a nucleotide sequence between samples. However, Kamb teaches that any method can be used to digest the target nucleic acid, Kamb states that uracil-N-glycosylase is one example of an enzyme that can be used for the digestion of the target nucleic acid, and Kamb teaches how to analyze a mixture of target nucleic acids that have been obtained by digestion with enzymes such as DNAse I. Additionally, the use of uracil-N-glycosylase to digest nucleic acids and to detect mutations was well known in the art, as exemplified by the teachings of McCarthy (discussed in the rejection below). In view of the teachings and guidance provided by Kamb and the knowledge in the art of how to use uracil-N-glycosylase to digest nucleic acids and to detect mutations, it would have been well within the skill of the art to have used uracil-N-glycosylase to generate the nucleic acid digestion products for MALDI-TOF analysis.

Applicants also traverse the rejection by asserting that Kamb does not provide any motivation to use MALDI TOF MS to distinguish a difference of one or more nucleotides between nucleic acids to be tested. Additionally, Applicants assert that Koster does not provide any motivation to use MALDI TOF MS in place of MALDI MS in the method of Kamb. These arguments are not convincing because for the purposes of combining references, those references need not explicitly suggest combining teachings much less specific references, In re Nilseen, 851 F. 2d 1401, 7 USPQ2d 1500 (Fed Cir. 1988). As stated in Ex parte Levengood, 28 USPQ2d 1300, "In order to establish a *prima facie* case of obviousness, it is necessary for the examiner to present *evidence*,

preferably in the form of some teaching, suggestion, incentive or inference in the applied prior art, or in the form of generally available knowledge, that one having ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention". Indeed, motivation for combining the teachings of the various references need not be explicitly found in the references themselves, but may be provided by the examiner based on logic and sound scientific reasoning. In the present situation, Koster (column 28) provides specific motivation to use MALDI TOF in place of MALDI MS because Koster teaches that MALDI TOF can distinguish between oligonucleotides that differ in length by one nucleotide and provides a fast and reliable means for analyzing nucleic acids.

Lastly, it is noted that Applicants response does not specifically address the rejection of claims 10-18 and 34 as these claims relate to a computer program which controls a method for detecting a difference of one or more nucleotides between a nucleic acid molecule. Applicants arguments regarding the length of the nucleic acid fragment or the means for digesting the nucleic acid do not distinguish the claimed computer programs over those suggested by the cited prior art. The claimed computer programs require only a computer means for controlling a method. As discussed in the above rejection, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have used a computer program to control the method of detecting a nucleotide variation in a nucleic acid sample in order to have provided a convenient and rapid means for storing and analyzing the data obtained from the detection method and / or for automating the detection method.

3. Claims 1-7, 10, 17,18, 24-30, 33-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb (U.S. Patent No. 5,869,242) in view of Koster (U.S. Patent 6,500,621) and further in view of McCarthy (WO 97/03210). In view of the amendments to change the dependency of the claims, this rejection now also applies to claims 11-16.

This rejection is based on the interpretation that the claims encompass methods in which uracil-N-glycosylase is used to directly detect the presence of a mutation and is used to cleave the sample nucleic acid at a site of nucleotide variation.

The teachings of Kamb and Koster are presented above. In particular, in combination Kamb and Koster teach a method to detect the presence of a nucleotide variation in a sample nucleic acid wherein the method comprises base specific digestion of the sample nucleic acid and analysis of the digested nucleic acids by MALDI TOF MS in order to compare the lengths and compositions of digested sample nucleic acids with reference nucleic acids. Kamb teaches that digestion may be performed "via any one of several techniques." Kamb (column 4, lines 36-41) also states that in one embodiment, it is beneficial "to incorporate deoxyuridine into amplified DNA. This is useful for producing small fragments by later digesting the amplified DNA with uracil-N-glycosidase." Kamb does not specifically teach using uracil-N-glycosidase to directly detect the presence of a mutation that alters a cleavage site.

McCarthy (see, for example, pages 8 and 13) teaches a method for detecting the presence of a mutation in a nucleic acid. In the method of McCarthy, PCR is performed in the presence of deoxyuridine triphosphate (dUTP) so as to generate an amplification product containing dUTP, the amplification product is treated with the enzyme uracil-N-

glycosylase in order to cleave the nucleic acid. The enzyme cleaves the nucleic acid between the base uracil and the sugar moiety of the DNA to generate an apyrimidinic site, which is subsequently cleaved to generate DNA fragments. Cleavage occurs only if dUTP has become incorporated into the nucleic acid molecule. In this way, the method is diagnostic for the presence of a T residue at a specific position in the DNA sequence and thereby assaying the cleavage products can be used to detect the presence of a mutation to a T residue in the nucleic acid. McCarthy (page 17) teaches that the DNA fragments are analyzed by "existing DNA sizing methods such as polyacrylamide gel electrophoresis, agarose gel electrophoresis or high performance liquid chromatography (HPLC)."

In view of the teachings of McCarthy, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kamb so as to have performed the cleavage reaction using uracil-N-glycosylase. The ordinary artisan would have been motivated to have used uracil-N-glycosylase in place of ribonuclease T1 or another cleavage reagent because McCarthy teaches that uracil-N-glycosylase can be used to specifically detect the presence or absence of a T residue at a specific location in a nucleic acid and thereby use of uracil-N-glycosylase in the method of Kamb would have provided an effective means for analyzing DNA samples for the presence of a mutation involving thymine.

RESPONSE TO ARGUMENTS:

In the response filed November 3, 2004, Applicants traversed the above rejection by arguing that McCarthy does not provide any teaching or motivation to use uracil-N-glycosylase to cleave nucleic acid molecules for analysis by MALDI-TOF.

Applicants arguments have been fully considered but are not persuasive because when taken as a whole, the combined prior art does in fact suggest using uracil-N-glycosylase to cleave nucleic acid molecules for analysis by MALDI-TOF. Specifically, Kamb teaches that the nucleic acids to be analyzed may be obtained by any digestion means and states that one means for digestion includes the use of uracil-N-glycosylase. McCarthy (see, for example, pages 8 and 13) teaches a method in which PCR is performed in the presence of deoxyuridine triphosphate (dUTP) so as to generate an amplification product containing dUTP and the amplification product is treated with the enzyme uracil-N-glycosylase so as to cleave the nucleic acid. McCarthy teaches that the method thereby allows for the specific cleavage of nucleic acids which have incorporated dUTP, and thereby distinguishes nucleic acids having a T residue from nucleic acids having a C, G or A residue. In view of the teachings of McCarthy, it would have been obvious to one of ordinary skill in the art to have used uracil-N-glycosylase in place of ribonuclease T1 or another cleavage reagent because McCarthy teaches that uracil-N-glycosylase can be used to specifically detect the presence or absence of a T residue at a specific location in a nucleic acid and thereby use of uracil-N-glycosylase in the method of Kamb would have provided an effective means for analyzing DNA samples for the presence of any mutation involving thymine. Further, when taken collectively, in view of the teachings of Koster, it would have been obvious

to one of ordinary skill in the art at the time the invention was made to have used MALDI TOF to analyze the uracil-N-glycosylase digestion products because Koster teaches that MALDI TOF can distinguish between oligonucleotides that differ in length by one nucleotide and provides a fast and reliable means for analyzing nucleic acids.

4. Claims 8, 9, 31 and 32 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kamb in view of Koster, or Kamb in view of Koster and further in view of McCarthy, as applied in paragraphs 3 and 4 above respectively, each further in view of Vestal (U.S. Patent NO. 6,057,543).

The teachings of Kamb in view of Koster and Kamb in view of Koster and McCarthy are presented above. The combined references do not teach further separation of the DNA fragments by post source decay.

Vestal teaches the use of post source decay in combination with MALDI TOF MS to analyze nucleic acids. Vestal states that "by suitable adjustment of the mirror potentials these fragment ions may be focused to produce a high quality post-source decay (PSD) spectrum which can be used to determine molecular structure. It is therefore a principal object of this invention to improve the performance of time-of-flight mass spectrometers, particularly in regard to applications involving production of ions from surfaces, by improving resolution, increasing mass accuracy, increasing signal intensity, and reducing background noise. It is another object to reduce the matrix ion signal in MALDI time-of-flight mass spectrometers. Another objective is to provide TOF mass spectrometers suitable for fast sequencing of biopolymers such as nucleic acids, peptides, proteins, and polynucleotides by the analysis of chemically or enzymatically

generated ladder mixtures. Still another objective is to utilize fast fragmentation processes for obtaining structural information on biomolecules such as oligonucleotides, carbohydrates, and glycoconjugates."

In view of the teachings of Vestal, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have modified the method of Kamb so as to have further separated the DNA fragments by post source decay in order to have improved the resolution and accuracy of the detection method and to have allowed for further analysis of the molecular structure of the DNA fragments.

RESPONSE TO ARGUMENTS:

In the response filed November 3, 2004, Applicants traversed the above rejection by arguing that none of the cited references provide the motivation to incorporate a further separation step to improve the sensitivity of detection. This argument is not convincing because Vestal provides the motivation to use PSD in combination with MALDI TOF. In particular, Vestal teaches that further separation of the DNA fragments by post source decay improves the resolution and accuracy of the detection method and allows for further analysis of the molecular structure of the DNA fragments.

Applicants assert that the claimed invention provides unexpected improved results because where longer oligonucleotides are fragmented, the chance of distinguishing between fragments is increased by further separation in a second dimension, such as by PSD. However, the improved results would have been expected because Vestal teaches that PSD analyzes the molecular structure of nucleic acids and improves the resolution and separation of nucleic acids.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
January 18, 2005

Carla Myers
CARLA J. MYERS
PRIMARY EXAMINER